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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,942	05/04/2005	Enrico Garaci	725.1046	9693

20311 7590 02/22/2010

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
02/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/533,942	GARACI ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-9 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/13/2010 has been entered.

Status of the Claims

2. Claims 4, 13, and 16 have been amended by the Applicant in correspondence filed on 01/13/2010. Claims 4-9 and 13-18 are currently pending. This is the first Office Action on the merits of the claim(s) following a request for continued examination.

RESPONSE TO ARGUMENTS

3. Claims 13 and 16 are objected to because of minor informalities. This objection is moot in light of Applicants' amendment to Claims 13 and 16.

4. Claims 4-9 and 13-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Root, et al. (Journal of General Virology, 2000), in view of Stewart, et al. (Biochemistry, 1999), and Heredia, et al. (Journal of Acquired Immune Deficiency Syndromes, 2000). Applicants traversed this rejection on the grounds that the combination of prior art does not teach or fairly suggest the claimed invention. Specifically, Applicants contend that Root, et al., teach that

reversible inhibition of PKC by bisindolylmaleimide 1.HCl inhibits entry of the influenza virus into the cell, whereas the instant claims are drawn to a non-reversible inhibition of PKC by resveratrol, which does not inhibit viral entry into the cell; rather, resveratrol inhibits "influenza virus replication" (emphasis in reply). Applicants assert that Stewart, et al., does not compensate for the alleged deficiencies of Root, et al., because Stewart, et al., discloses the anti-cancer activity of resveratrol. Thus, there is no motivation to combine the teachings of Root, et al., and Stewart, et al. Applicants disagree with the application of Heredia, et al., because this art is drawn to inhibiting HIV replication, not influenza replication, and that the skilled artisan would not reasonably predict that anti-HIV drugs would be efficacious for treating influenza. Applicants also do not agree with Examiner's contention that the art worker would be motivated to use resveratrol because of its low cost and safety. Applicants point to Heredia, et al., as evidence that resveratrol has low activity, and to Stewart, et al., as evidence of its toxicity in mammals. Respectfully, Examiner does not find Applicants' arguments persuasive.

5. "Influenza virus replication" is not defined in the instant claims or the specification. Thus, one of ordinary skill in the art would reasonably interpret "influenza virus replication" to encompass any disruption of the viral life cycle, such as inhibiting entry into a target cell. If a virus cannot enter a target cell, the virus can not replicate, and, thus, influenza virus replication is inhibited. Applicants have not disputed this interpretation of "influenza virus replication."

6. Root, et al., explicitly teach bisindolylmaleimide 1.HCl inhibits viral replication in a dose-dependent manner, and that "PKC is crucial for influenza virus entry and may be a target for antiviral therapy" (pg 2698, paragraph spanning cols 1 and 2). This provides motivation for the art worker to use PKC inhibitors for the treatment inhibition of influenza virus replication.

That bisindolylmaleimide 1.HCl inhibits entry of the influenza cell into target cells in a reversible manner is not a persuasive argument because Root, et al., clearly state that inhibition of PKC in general, not reversible inhibition specifically, effectively inhibits influenza virus replication by denying entry of the virus into the target cell. Applicants have provided no evidence or rationale suggesting that the direct effect of reversible inhibition of PKC is distinct from non-reversible inhibition with respect to precluding the entry of influenza virus into a target cell. Taken together, Root, et al., suggests that PKC inhibitors (reversible or nonreversible) would be effective for inhibiting influenza virus replication. Root, et al., does not directly link resveratrol to PKC inhibition or inhibition of influenza virus replication.

7. Stewart, et al., explicitly disclose that resveratrol is a PKC inhibitor. Indeed, Stewart, et al., teach that resveratrol "potently inhibits" cellular PKC at a concentration of 15 μM (pg 13249, col 2, para 1, lines 4-5). Stewart, et al., do not discuss the role of PKC or resveratrol on influenza virus. Thus, Stewart, et al., provides only that resveratrol inhibits PKC. In the absence of unexpected results, the art worker would reasonably expect that resveratrol would inhibit PKC in both cancer and non-cancer cells (i.e. cells that are potentially infected by the influenza virus). Taken together, Root, et al., and Stewart, et al., suggest that resveratrol, by inhibiting PKC, would be an effective inhibitor of influenza virus replication (by inhibiting viral entry into the target cell) and treatment for influenza virus infection.

8. Heredia, et al., explicitly teach the virtues of resveratrol (i.e. low cost, established safety profile). The skilled artisan would be motivated to use naturally occurring resveratrol because it is already generally regarded as safe and can be obtained relatively easy and inexpensively. That Heredia, et al., discusses the ability of resveratrol to treat HIV does not negate the stated

advantages with respect to drug development. Examiner agrees that low cost alone may not be sufficient motivation to use resveratrol as an anti-influenza agent. However, Applicants' doubts regarding the art recognized efficacy and safety are overstated. Heredia, et al., explicitly teaches that resveratrol is "widely used" and can be nontoxic (pg 247, col 1, final paragraph). Moreover, the discussion in Stewart, et al., about the toxic effects of resveratrol relate to doses of resveratrol that are sufficient to inhibit "a broad spectrum of protein kinases" (pg 13249, col 2, para 2, lines 10-17), not specifically inhibiting PKC. For treatment of influenza infection, or inhibiting the virus's replication, Root, et al., and Stewart, et al., teach that inhibition of a broad spectrum of protein kinases is not necessary to exert anti-influenza virus efficacy. Instead, all that is required is inhibition of PKC, which can be achieved at a sub-toxic dose of resveratrol.

9. Applicants also argue that reversible inhibition of PKC by bisindolylmaleimide 1.HCl inhibits entry of the influenza virus into the cell, whereas the instant claims are drawn to a non-reversible inhibition of PKC by resveratrol, which does not inhibit viral entry into the cell; rather, resveratrol inhibits "influenza virus <u>replication</u>" (emphasis in reply). Applicants may be suggesting that "influenza virus replication" is distinct from inhibition of viral entry into the cell, for example, inhibiting replication of viral DNA. As discussed earlier, this distinction is not made either in the instant claims or in specification. Thus, inhibiting influenza virus replication reasonably encompasses inhibition of viral entry into the target cell. Regardless, even if such a distinction were made, the prior art provides a method of using resveratrol for the treatment of influenza virus infection (discussed above). The art worker would be motivated to use resveratrol, a known PKC inhibitor, for the treatment of influenza virus infection, and would reasonably predict that the mechanism of action of this treatment would be a denial of cellular

entry of the influenza virus. Applicants' discovery that resveratrol has a different mechanism of action is not sufficient to render the claimed invention nonobvious over the prior art (see *In re Wiseman* and MPEP §2145(II)).

10. For the above reasons, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use resveratrol to non-reversibly inhibit influenza virus replication. Therefore, the rejection of Claims 4-9 and 13-18 under 35 U.S.C. 103(a) as being unpatentable over Root, et al., in view of Stewart, et al., and Heredia, et al., is maintained.

Conclusion

11. Claims 4-9 and 13-18 remain rejected.

12. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/San-ming Hui/
Primary Examiner, Art Unit 1628